HCRC
Hepatitis C Resource Centers

Treatment Recommendations for Patients with Chronic Hepatitis C

Veterans Health Administration

Treatment Recommendations for Patients with Chronic Hepatitis C: 2002 Version 3.0

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I. Background

Hepatitis C (HCV) is a chronic viral infection that rarely resolves spontaneously. The prevalence of hepatitis C is believed to be at least 1.8% in the United States general population. Persons aged 40 to 59 years (which includes the age group of veterans who served in the Vietnam era) have the highest prevalence of HCV infection, and in this age group, the prevalence is highest in African Americans (6.1%). The prevalence of HCV infection in veterans who currently use Veterans Health Administration's Medical Facilities is believed to be higher than the general U.S. population.

In acute infection, HCV RNA is detectable in blood within 1 to 3 weeks after exposure, and by three months, antibodies to hepatitis C (anti-HCV) are present in 90% of patients. Approximately 85% of individuals with acute infection progress to chronic infection, the majority with evidence of liver disease (either elevated serum ALT and/or abnormal liver histology). Approximately 15-20% of patients with chronic infection develop cirrhosis. However, the natural history of HCV disease is highly variable, with some patients progressing to cirrhosis in 15 years, and others never progressing to cirrhosis over a life-time.[1] Moreover, the incidence of hepatocellular carcinoma, one of the complications of late stage HCV infection, is rising, increasing the need for therapeutic interventions in this patient population.

Treatment for hepatitis C includes steps to slow disease progression, to prevent complications of cirrhosis, and to treat complications of chronic HCV infection. Anti-viral therapy with interferon-based regimens results in eradication of viral replication (sustained virological response) in some patients. Because currently approximately 50% of treated patients do not achieve a sustained virological response, treatments for HCV disease remain inadequate, regardless of the dose and duration of treatment. Interferon-based therapies must be administered parenterally, which represents a potential barrier to care, and interferon has significant side effects, which further limits the willingness of patients to undergo treatment. In view of the variable natural history, the frequency of therapy-related toxicity and the lack of uniform benefit, anti-viral treatment has the greatest potential benefit for those at greatest risk of progressive liver disease and/or their quality of life is reduced from chronic infection. In addition, a substantial number of patients have clinical conditions considered contraindications to interferon treatment. Many of these contraindications are based on limited data as well as clinicians' personal assessments. Thus, there is considerable potential for arbitrarily limiting treatment options for the large group of HCV patients with psychiatric or addictive disorders.[2,3] More research is needed to identify appropriate treatment for these as well as for other patients not currently considered treatment candidates. The following guidelines are based on recommendations of the NIH Consensus Development Conference in 2002, review of published data, the CDC recommendations for the identification, counseling, testing, and referral of persons at risk for HCV infection, and the input of thought leaders involved in the care of veterans with HCV infection.[4,5] The recommendations have been updated since the FDA-approval of peginterferon alfa 2b (12kD) plus ribavirin and peginterferon alfa 2a (40kD) and since the NIH Consensus statement in June 2002.

II. Management of Patients with Hepatitis C

Management of patients who are anti-HCV positive by ELISA should include

- confirmation of chronic infection using appropriate laboratory tests for confirmation of antibody status and/or detection of viremia;
- notification of test results with appropriate counseling;
- education regarding factors which increase the risk of progressive liver injury (alcohol, medications);
- counseling on modes of transmission of HCV, including parenteral and sexual transmission;*
- medical assessment regarding need for vaccination against hepatitis A and B;
- evaluation for potential antiviral therapy;
- testing for HIV infection.

In order to determine the need for therapy, patients with chronic HCV infection should be assessed for:

- biochemical evidence of chronic liver disease by elevation of serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST);
- severity of disease and possible treatment according to current practice guidelines in consultation with, or referral to, a specialist knowledgeable in this area;
- liver biopsy which, although not essential, is recommended (see **Section IV**);
- adequate hemoglobin, white blood cell, and platelet counts to tolerate therapy (see **Section IV**);
- measurement of hepatic synthetic function (serum albumin, bilirubin, prothrombin time);
- determination of potential contraindications to therapy.

*Additional information regarding diagnosis of hepatitis C, counseling guidelines, testing for hepatitis C viral RNA, and interpretation of liver histology in HCV disease is available at http://www.va.gov/hepatitisc

III. Selection of Patients for Treatment

All patients with chronic hepatitis C are potential candidates for therapy. However, given the current limitations of therapies, treatment is more clearly recommended in some patients. In others, decisions should be made on an individual basis or within the context of clinical trials. Decision to treat should include discussion with the patient about the benign natural history in the majority of patients with HCV infection.

III:A. The group in which treatment is clearly indicated

- Patients with histologically moderate disease and those with compensated cirrhosis

The NIH Consensus Development Conference determined that treatment is recommended for patients with chronic hepatitis C who are at greatest risk for progression to cirrhosis.[4] These are patients with detectable serum HCV RNA and liver histology showing hepatic fibrosis. Most patients in this group have persistently or intermittently elevated ALT values. Good response is achievable in patients with significant fibrosis including cirrhosis,[6-9] although patients with bridging fibrosis and/or cirrhosis appear to respond less well to therapy than patients with minimal or no fibrosis.[9,10] Data on treatment of patients with compensated cirrhosis are largely derived from sub-group analyses of clinical trials, and there have been few prospective studies focused on this population alone. An important goal of treatment of patients with compensated cirrhosis is delay in histological disease progression and prevention of clinical complications of disease, goals that are currently being evaluated in the NIH-sponsored HALT-C trial. Patients with compensated cirrhosis are therefore candidates for therapy. Given other clinical indications, patients with substance abuse who have been stabilized with appropriate addiction treatment should also be considered as candidates for HCV therapy. Patients can be successfully treated while on methadone maintenance for opioid dependence.[11] Recently updated guidelines from the National Institutes of Health[4] indicate that efforts should be made to increase the availability of best current treatment to patients with substance use disorders (injection drug use, alcohol abuse) and those with co-morbid medical and neuropsychiatric conditions. Ideally, if therapy is given to such patients, treatment should be administered in collaboration with addiction specialists and other mental health professionals, due to increased risk of relapse to substance abuse (http://consensus.nih.gov/cons/116cdc_intro.htm).

III:B. The groups in which treatment is less clearly indicated

Treatment is less clearly indicated in the following groups, because (i) liver disease is mild and/or (ii) there is concern about the safety of interferon plus ribavirin, and/or (iii) data supporting treatment are limited:*

- Patients with histologically mild disease

  Patients in whom the liver biopsy demonstrates Grade 1 inflammation without evidence of fibrosis (see http://www.va.gov/hepatitisc/pved/liverbiopsy_histopathology.htm) are at low risk of progression to cirrhosis, and the majority will never develop advanced liver disease. In such patients, and following discussion of the natural history and treatment with the patient, the physician may elect to observe without treatment. During observation, serum ALT should be measured periodically, and liver biopsy should be repeated in 3-5 years, particularly if serum ALT is persistently abnormal. If liver disease has progressed, treatment could be reconsidered at that time. Treatment may be provided to patients with mild liver disease who seek intervention or who have significant

extrahepatic HCV symptoms. However, exposure of patients to side effects of therapy may be unnecessary, given the benign nature of the disease. Thus, risks and benefits should be thoroughly discussed with each patient.

- Patients with normal serum ALT
  Approximately 30% of patients with chronic hepatitis C have normal serum ALT levels. A persistently normal ALT does not preclude histological evidence of liver injury, but injury is in general more mild than that observed in patients with an elevated ALT. Experts differ as to whether to perform liver biopsy and to treat these patients. Factors influencing the decision to treat should include favorable genotype, presence of hepatic fibrosis, patient motivation, symptoms, severity of co-morbid conditions and the patient's age.[4] To make an informed decision regarding need for treatment, liver biopsy may need to be performed in patients who lack contraindications to therapy. Limited data that exist regarding the response to interferon plus ribavirin in these patients suggest that sustained virological response (SVR) does not differ in patients with normal or mildly elevated serum ALT versus those with clearly elevated serum ALT.[4] Studies of peginterferon plus ribavirin have not been completed in patients with normal ALT levels. Patients with significant hepatic fibrosis (stage II or higher) may be at risk for progressive liver disease and as such should be considered for therapy. Patients with minimal or no fibrosis on liver biopsy may be reassured about their favorable prognosis and may choose to defer therapy.[4]

- Patients over the age of 60 or those with significant non-hepatic disease
  Given the long interval between infection and the development of complications of liver disease as well as the variability in the natural history of infection, treatment is not routinely indicated in patients who are over the age of 60 years or who have significant disease other than liver disease (such as symptomatic coronary artery disease, uncontrolled diabetes, renal insufficiency, and symptomatic chronic obstructive pulmonary disease). In these individuals, the reduced life expectancy from the underlying condition, as well as the potential for increased side effects from hepatitis C treatments, should be taken into account when determining the potential benefits of treatment. However, age greater than 60 years *per se* does not preclude treatment in patients who are in otherwise good health.

- Patients who have undergone solid organ transplantation
  Limited data exist regarding the risks and benefits of treatment in patients who have undergone solid organ transplantation. Preliminary results from case series on the efficacy of interferon plus ribavirin or peginterferon in liver allograft recipients suggest that SVR is lower than in immune competent individuals. The tolerability of ribavirin appears to be less than in immune competent individuals because of a higher prevalence of anemia and renal insufficiency in transplant recipients. In recipients of renal or cardiac allografts, interferon is generally contraindicated because of an increased risk of precipitating severe allograft rejection. This risk of rejection appears to be lower in recipients of liver allografts.

- Patients with HCV/HIV coinfection
  All patients with HIV should be tested for hepatitis C and all patients with hepatitis C infection should be offered HIV testing. Patients infected with both HIV and hepatitis C appear to be at higher risk of liver disease progression than those with HCV infection

alone. Therefore, they should be seriously considered for HCV therapy.[12] Thus far, studies have only enrolled patients with stable HIV infection and well-compensated liver disease.[4] Treatment outcomes with either interferon or peginterferon plus ribavirin are not yet well defined, although preliminary data suggest better response with peginterferon with ribavirin than with standard interferon plus ribavirin.[4] These patients may have reduced tolerance of ribavirin because of anti-retroviral-associated anemia. There are also reports of lactic acidosis occurring in coinfected patients receiving anti-retroviral as well as ribavirin therapy,[13,14] possibly due to interactions between ribavirin and HIV antiretrovirals such as ddI and d4T.

- Patients with acute hepatitis C

  Acute hepatitis C is rarely recognized and diagnosed. Studies of interferon treatment for acute hepatitis C have been very heterogeneous and limited by small sample size, lack of randomization, differences in dose and schedule, and differences in endpoints and follow-up. Although high SVRs have been seen in small uncontrolled trials with interferon monotherapy, recommendations on whether treatment is necessary, the timing of treatment and the regimen to use, remain open.[4,15] In the absence of such data, it seems appropriate to treat patients with acute hepatitis C[4], probably with combination therapy.

- Patients with active injection drug use and with histologically moderate disease or compensated cirrhosis

  Patients with prior or ongoing injection drug use comprise the largest group of individuals with hepatitis C in the U.S. Successful treatment of such patients has the potential not only to benefit the individual but also to prevent transmission to others. Results from a recent small trial have demonstrated the feasibility and effectiveness of treating HCV in people who recently used illicit injection drugs and who were enrolled in a monitored drug treatment program.[16] The results from this small trial may be difficult to reproduce in other settings or with larger populations. If treatment in this group is undertaken, it should be administered with close collaboration between hepatitis C providers and substance abuse specialists.

- Patients with ongoing alcohol use and with histologically moderate disease or compensated cirrhosis

  Alcohol is an important co-factor in progression of HCV disease to cirrhosis and hepatocellular carcinoma.[4] A history of alcohol abuse is not a contraindication to therapy. Limited data suggest that heavy alcohol consumption of > 80g/day compromises response to hepatitis C therapies. Effects of lower levels of alcohol consumption on treatment response are less clear.[4] Ideally, patients with active alcohol use/abuse should be treated for their addiction successfully, before the initiation of therapy.

- Patients with complications of advanced disease

  Once patients develop clinical complications of cirrhosis (gastroesophageal bleeding, ascites, encephalopathy, impaired hepatic synthetic function, hepatocellular carcinoma), liver transplantation is the treatment of choice. There are limited data treating such patients with low doses of interferon and ribavirin.[4] Typically, these patients respond poorly to treatment and may be at risk for further hepatic decompensation (http://consensus.nih.gov/cons/116cdc_intro.htm). Moreover, because of associated

cytopenias in this group, dose reductions/discontinuations are frequent. Patients with decompensated liver disease are also at risk for life-threatening infections, and this risk may be increased further by the administration of interferon-based therapies with associated leukopenias. If treatment with interferon-based therapies is undertaken, such patients should be enrolled in research protocols, preferably with liver transplantation available should the clinical condition of the patient worsen further on therapy (see http://www.va.gov/hepatitisc/pved/livertransplant.htm).

Given the inadequacy of data regarding the benefits of treatment in these groups, when possible, these patients should be treated within the context of a therapeutic clinical trial.

IV. Assessment of patients prior to initiating anti-viral therapy.

Necessary and recommended assessments for patients with chronic hepatitis C are summarized in **table 1**.
Contraindications to hepatitis C therapy are summarized in **table 2**.
A comparison of the HCV RNA quantitative assays are summarized in **table 3.**
FDA-approved therapies for hepatitis C disease are summarized in **table 4**.

All patients with confirmed, chronic HCV infection should be evaluated for possible treatment with an anti-viral regimen. Due to the limited efficacy and substantial potential toxicity of these regimens, each patient needs a careful assessment to determine the relative risks and benefits of beginning therapy immediately, delaying consideration of therapy until a later time, or deferring therapy indefinitely. The following should be performed in all patients as part of that assessment:

- Evidence of liver disease
  All patients must have evidence of HCV-associated liver disease (abnormal transaminase levels and/or histologic evidence of liver damage), with preserved hepatic synthetic function as indicated by a normal or near normal serum albumin, direct serum bilirubin, and prothrombin time, unless abnormalities can be explained by conditions other than liver disease.

- Laboratory tests
  (i) Patients should have a platelet count > 75k/mm^3 and an absolute neutrophil count > 1.5 k/mm^3 in order to tolerate therapy. Patients with platelets and absolute neutrophil counts below these cut-offs may be started on therapy, but will typically require dose reductions and may not be able to receive sufficient therapy to derive benefit.
  (ii) Patients who will receive ribavirin as part of their therapy must have an adequate hemoglobin ($\geq$13 g/dL for men and $\geq$ 12 g/dL for women) as well as normal renal function (creatinine $\leq$ 1.5 mg/dL).
  (iii) Patients must have serum HCV RNA quantified by such assays as the Roche Amplicor Monitor™, NGI Superquant assay™, or Bayer Versant™ assay (bDNA). Information regarding the viral load may aid in counseling patients as to their likelihood of response. Patients with low viral load are more likely to respond to treatment than those with high viral load; however, there is neither an absolute predictor of response nor non-response based on HCV RNA load. The definition of “low” and “high” viral load is somewhat arbitrary, but a “cut-off” of 800,000 IU/L is generally believed to be the value that allows distinction between these two groups. Prior to therapy, quantitation of HCV RNA, rather than mere detection by a qualitative assay, also allows measurement of reduction in HCV RNA with therapy (one or two log drops), which may in turn provide the clinician with information about response (or failure of response) to treatment. For consistency, the same quantitative assay should be used throughout the course of therapy. The relative conversion rates of the common quantitative HCV RNA assays from copies/ml to IU/L are included in **table 3**. These conversion numbers are not linear and should only be used for an approximate calculated conversion. For more information about HCV RNA assays see http://www.va.gov/hepatitisc/pved/labtests_HCVRNA.htm.

(iv) Patients should have pre-treatment testing for HCV genotype. The infecting genotype is an important predictor of sustained virologic response rates with all regimens (**tables 6, 7, 8,11,12**), and determines the duration of treatment.

- Assessment of psychiatric disease
  All patients should undergo evaluation for psychiatric disorders, particularly depression and suicide risk. Uncontrolled depression is an absolute contraindication to interferon-based therapies. Psychiatric disorders in remission or stabilized on treatment are not contraindications to interferon treatment but usually necessitate the involvement of a mental health professional during anti-viral therapy.

- Assessment for substance use
  All patients should undergo careful evaluation for current substance use disorders. Cessation of alcohol use is considered to be of prime benefit in slowing the progression of liver disease. Current heavy alcohol use (>14 drinks/week for men, or >7 drinks/week for women, or >4 drinks per occasion monthly or more frequently)[17], or active injection drug use are major concerns before beginning treatment, and such patients should be referred to an addiction specialist. Establishing abstinence prior to initiating treatment is recommended. However, patients stabilized in treatment, such as methadone maintenance, should be considered for interferon-based therapy.

  Urine toxicology for injectable drugs (opiates, cocaine, amphetamines) may also be used to supplement patient self-report. Non-injection drug use may, in theory, pose an obstacle to treatment adherence, but each case should be evaluated individually. Substance use disorders in full remission are not a contraindication to interferon treatment, although such patients may require additional monitoring and the coordination of care with addiction specialists.

- Assessment for compliance/adherence
  Patients should be assessed for likelihood that they will be able to adhere to treatment recommendations. Predicting adherence is difficult, but evidence of prior non-adherence with medical, psychiatric, and addiction therapies may indicate the need for careful attention to adherence during HCV treatment. Patients should be asked about their understanding of the treatment and their readiness to make the necessary lifestyle changes to ensure adherence with prescribed regimens. Also, adherence to the pre-treatment evaluation, the availability of social support systems, and the presence of an adequate environment for storage and administration of interferon should be assessed.

- Evaluation for autoimmune and other non-hepatic disorders that might complicate therapy
  Patients should be evaluated for autoimmune disorders. Because interferon can aggravate underlying non-hepatic, particularly autoimmune disorders, patients must be euthyroid (on replacement therapy if necessary) and diabetes, if present, must be controlled (normal or near normal serum hemoglobin A1C). Patients with stable or controlled psoriasis, rheumatoid arthritis, and other autoimmune diseases can be treated but should be monitored closely for signs of worsening disease. Patients should also be assessed for coexistent autoimmune liver disease with a serum ANA, and, if present in high titer, treatment should be administered with caution. However, in the absence of

other clinical evidence of autoimmune disease, detectable serum ANA, even if at high titer, does not pose a contraindication to therapy.

- Evaluation for hepatitis A and B immunizations
  Patients should be tested for HBsAg, anti-HBc (total), anti-HBs, and anti-HAV to evaluate need for hepatitis immunization.

- Assessment for other causes of liver disease
  Serum ferritin should be obtained to evaluate for hemochromatosis, a treatable liver disease.

- Assessment for pregnancy
  A pregnancy test for women of childbearing age should be obtained within a reasonable time before the initiation of treatment.

- Assessment of ocular function
  An ophthalmic exam should be performed at baseline in patients with risk factors for retinal disease (hypertension, diabetes) to identify any disease that might worsen with ribavirin or interferon therapy.

- Staging of liver disease
  Liver biopsy (http://www.va.gov/hepatitisc/pved/liverbiopsy_histopathology.htm) is the best method for determining the severity of liver injury (i.e. fibrosis stage of disease).[1] Liver biopsy may be helpful in excluding other causes of liver disease although this can be accomplished with reasonable accuracy by a careful history, physical examination, and appropriate laboratory testing. In patients with genotype non-1 infection, in whom likelihood of SVR with treatment is high (70 to 80%), the physician and patient may choose to initiate therapy regardless of the severity of liver disease. In this case, the findings from liver biopsy may not influence the treatment decision.

Table 1. Pre-Treatment Assessments in a Patient with Chronic Hepatitis C

Necessary

- Medical history, including the determination of complications of liver disease, significant extrahepatic disease, and symptoms associated with chronic HCV which may reduce quality of life
- Psychiatric history, including the determination of past or ongoing psychiatric and substance use disorders, previous and current treatments and response
- Biochemical markers of liver injury and assessment of hepatic synthetic function {serum ALT, serum albumin, serum bilirubin (particularly direct bilirubin), prothrombin time}
- Hemoglobin, hematocrit, total white cell count, differential, and platelet count
- TSH
- Serum glucose or HgbA1C in diabetics
- Pregnancy test (necessary for women of child-bearing potential)
- Serum HBsAg
- HIV serology
- Quantitative HCV RNA measurement by qPCR or bDNA
- HCV genotype
- Anti-HBc (total), anti-HBs, anti-HAV total
- Electrocardiogram in patients with pre-existing cardiac disease
- Validated screening instruments for depression[18,19] and alcohol use[20]
- For patients with diabetes and/or hypertension, an eye exam to evaluate for retinopathy

Highly Recommended

- Liver biopsy to stage the severity of liver disease (especially in patients with genotype 1 infection)
- Serum ferritin and serum ANA
- Urine toxicology screen for opiates, cocaine, and amphetamines

Table 2. Contraindications to Hepatitis C Therapy
• Life-determining extrahepatic disease (e.g. malignancy, unstable angina, severe COPD) • Clinically decompensated liver disease* • Uncontrolled autoimmune disorders • Pregnancy or planned pregnancy in a patient or the patient's sexual partner or unwillingness to use adequate birth control • Documented serious non-adherence to prior medical treatment or the failure to complete HCV disease evaluation appointments and procedures • Inability to self-administer parenteral medication or to arrange appropriate administration of parenteral medication • Severe uncontrolled psychiatric disease, particularly depression with current suicidal risk • Recent injection drug use • Ongoing alcohol abuse**

* Select patients with clinically decompensated disease may be candidates for treatment in research protocols

** Definitions of alcohol abuse in HCV disease are evolving and await further data. The NIH Consensus Statement concluded "Continued alcohol use during therapy adversely affects response to treatment, and alcohol abstinence is strongly recommended before and during antiviral therapy"[4]

Table 3. Comparison of HCV RNA Quantitative Assays	
Assay	**Copies/ml = 1 IU/L**
Abbott LCX HCV-RNA	3.8
Bayer bDNA 3.0	5.2
NGI Superquant	3.4
Roche Amplicor Monitor 2.0	2.4

V. Definition of Response

Efficacy of treatment is measured biochemically (defined as normalization of serum ALT), virologically (defined as undetectable serum HCV RNA), and histologically (defined as reduction in liver inflammation and/or fibrosis on post-treatment liver biopsy). Because treatment decisions are not altered by changes documented on post-treatment liver histology, post-treatment liver biopsy is not routinely recommended. Treatment endpoints are measured at two time-points: end-of-treatment response (ETR) and sustained treatment response (SVR), the response 6 months post-treatment. Biochemical and virological improvements are typically associated with histological improvement. Throughout the rest of this document, ETR will be used to designate an end-of-treatment virological response and SVR to designate a sustained virological response. Recently, data have been reported regarding the utility of "on-treatment response" or "early virological response" (EVR) measured at 12 weeks (defined as undetectable HCV RNA or a two log reduction of HCV RNA from pre-treatment value) in predicting SVR.[4,21] Failure to achieve EVR is a strong predictor of ultimate non-response. Less than 2% of patients who failed to achieve an

EVR, but continued on therapy had an SVR.[21] Thus the physician and the patient may choose to discontinue therapy in patients who have failed to achieve this viral drop.
EVR cannot be adequately assessed if different assays are used for baseline and 12-week measurements of HCV-RNA or if the baseline value is outside the range of reliable quantification for the assay being used.

VI. Current Anti-viral Treatments (Table 4)

VI:A. Therapies for treatment naïve patients

The current standard of care for most patients with chronic hepatitis C disease is pegylated interferon plus ribavirin.[4] There remain sub-groups of patients in whom the optimal therapy remains undefined and for whom standard interferon plus ribavirin or peginterferon monotherapy may be acceptable alternatives. These sub-groups are discussed in section **VI:A** (ii).

(i) Pegylated Interferons

Pegylation of interferon (linking the interferon to a molecule of polyethylene glycol, PEG) reduces the clearance of the interferon compared with the standard formulation. The length of the polyethylene glycol molecule and the method of linkage between the PEG and the interferon alter the pharmacological properties of the molecule. Peginterferon alfa 2b (12 kD) is FDA approved both as a monotherapy and in combination with ribavirin.[8,9] Peginterferon alfa 2a (40kD) is also approved as a monotherapy. Comparison of the pharmacological properties of both pegylated products is shown in **Table 5**.

Peginterferon plus the oral antiviral agent ribavirin was compared to standard interferon plus ribavirin in a clinical trial with three treatment regimens:

1. Peginterferon alfa 2b (12 kD) (1.5 µg/kg qw) plus ribavirin (800mg qd)
2. Peginterferon alfa 2b (12 kD) (1.5 µg/kg qw with a reduction to 0.5 µg/kg qw after 4 weeks) plus ribavirin (1000-1200 mg qd), and
3. Standard interferon alfa 2b plus ribavirin[9]

There was no difference in the SVR between the lower dose of peginterferon alfa 2b (12 kD) plus ribavirin and standard interferon alfa 2b plus ribavirin.[8,9] The difference in the overall treatment response between peginterferon alfa 2b (12 kD) (1.5 µg/kg) plus ribavirin and interferon alfa 2b plus ribavirin was 6% with a 95% confidence interval of 0.18 to 11.63, adjusted for viral genotype and presence of cirrhosis at baseline.[8]

The overall response and the response stratified by genotype, as listed in the product insert[8] and reported by Manns et al,[9] are summarized in **table 6A**. As with other interferon-based therapies, patients with genotype 1 infection, regardless of their pretreatment viral load, had a lower response to peginterferon alfa 2b (12 kD) plus ribavirin compared to patients infected with other viral genotypes (**table 6A**).[8] The superior efficacy of peginterferon plus ribavirin over standard interferon plus ribavirin was seen in patients with genotype 1 infection (**table 6A**). Patients with both genotype 1 infection and a high viral load (> 2,000,000 copies/mL, >800,000 IU/mL) had a response of 30% (78/256) compared to a response of 29% (71/247) with interferon alfa 2b plus ribavirin.[8] No difference was demonstrated in efficacy of peginterferon plus ribavirin compared with standard interferon

plus ribavirin in patients with bridging fibrosis and/or cirrhosis (**table 6B**). Sub-group analyses of response by genotype and by stage of liver fibrosis were constrained by sample sizes that may not have provided sufficient statistical power to demonstrate a clinically meaningful difference.

Independent variables associated with a favorable response to peginterferon plus ribavirin included genotype non-1, low pre-treatment HCV RNA level, lighter body weight, younger age, and the absence of bridging fibrosis/cirrhosis.[9] Occurrences of adverse events were similar between those patients receiving peginterferon plus ribavirin and those receiving interferon plus ribavirin, except for a higher frequency of injection site reactions (75% versus 49%) and a higher frequency of neutropenia with the pegylated product (26% versus 14%).[8]

Peginterferon alfa 2b (12 kD) (1.5 µg/kg qw) in combination with ribavirin (800 mg qd) was the regimen that received FDA approval.

There has been much discussion about the appropriate dose of ribavirin administered in combination with peginterferon alfa-2b. The FDA-approved dose at 800 mg is lower than that approved for standard interferon alfa-2b. The dose was selected for the prospective trial establishing the safety and efficacy of peginterferon alfa-2b in combination with ribavirin because of concerns about potential additive toxicities of peginterferon at high dose and ribavirin at "standard dose". Subsequent data from trials of peginterferon alfa 2a have suggested that the 800 mg dose is sufficient for treatment of genotype non-1 infection, but that higher doses (1000 mg/1200 mg based on a 75 kg weight) are necessary for effective treatment of genotype 1.[22] For further discussion about ribavirin dosing see section VI:A (iii).

Peginterferon alfa 2a (40 kD) has recently been licensed as monotherapy. While the interferon molecules alfa 2a and alfa 2b are similar, there are differences in the way that these two proteins are linked to polyethylene glycol as well as differences in the size of the polyethylene glycol molecule (12 kD versus 40 kD). These differences alter their pharmacokinetic and pharmacodynamic properties (**table 5**).

The safety and efficacy of peginterferon alfa 2a (40 kD) have been compared directly with interferon alfa 2a in treatment naïve patients with chronic hepatitis C[23] (**table 7A**) as well as in treatment naïve patients with cirrhosis or transition to cirrhosis from chronic hepatitis C[24] (**table 7B**).

Note:
Several of the recommendations in this document are derived from data generated with pegylated interferon alfa 2a plus ribavirin and comparable data do not exist in patients receiving pegylated interferon alfa 2b plus ribavirin.

These include recommendations for

- treatment duration for patients with genotype non-1 infection

- use of a 12 week rather than a 24 week time point for determination of early virological response (EVR)
- dosing with 1000/1200mg of ribavirin for genotype 1 and 800mg for genotype non-1

We acknowledge the scientific limitations of making the “transfer” of findings obtained with one pegylated product to the use of another, but feel that in the absence of additional information or information that may not be forthcoming, such “transfer” serves the best interests of our patients.

Table 4. FDA Approved Treatments for Chronic Hepatitis C		
Generic; Trade name	**Recommended Dose**	**Major Adverse Effects***
Interferon (IFN) • alfa-2a; (Roferon-A®) • alfa-2b; (Intron A®) • alfacon-1; (Infergen®)	3 MU tiw 3 MU tiw 9 µg tiw	• Flu-like symptoms • Bone marrow suppression • Aggravation of autoimmune disorders • Neuropsychiatric symptoms • Seizures • Acute cardiac and renal failure • Retinopathy • Interstitial pulmonary fibrosis
IFN alfa 2b + Ribavirin (Rebetron®)	IFN alfa 2b 3 MU tiw and if *Pt wt ≤ 75 kg* RBV 1,000 mg daily or if *Pt wt >75 kg* RBV 1,200 mg daily	• Adverse effects of IFN • Hemolytic anemia • Significant teratogen • Rashes • IFN + RBV -> GI effects
Peginterferon alfa 2b – 12 kD (PEG-Intron®)	Weekly dose of 1.0 µg/kg SC	• Adverse effects similar to interferon alfa 2b • More frequent injection site reactions and neutropenia with peginterferon compared to interferon alfa 2b
Ribavirin (Rebetol®)	<u>Genotype 1:</u> if *Pt wt ≤ 75 kg* RBV 1,000 mg daily po or if *Pt wt >75 kg* RBV 1,200 mg daily po <u>Genotype 2,3:</u> 800 mg daily po	• Hemolytic anemia • Significant teratogen • Rashes • Headaches • Shortness of breath • GI side-effects
Peginterferon alfa 2b - 12 kD + Ribavirin (PegRebetron®)	Weekly dose of 1.5 µg/kg SC RBV 800 mg po daily Higher doses of RBV may be beneficial in genotype 1	• Side effect profile similar to interferon plus ribavirin • Greater frequency of injection site reactions and neutropenia
Peginterferon alfa 2a (40kD) (Pegasys®)	Weekly dose of 180µg SC regardless of weight	• Adverse effects similar to interferon alfa 2b, interferon alfa 2a and peginterferon alfa 2b.

** Adverse effects included are limited to those reported in highest frequency in placebo-controlled studies, or are of sufficient severity to warrant discontinuation of therapy and/or treatment of the adverse effect(s). Consult other references for complete listing of reported adverse effects.*

Table 5. Comparative Pharmacokinetics of Pegylated Interferons			
	Interferon alfa	**Peginterferon alfa 2b (12kD) Glue et al[25]**	**Peginterferon alfa 2a (40kD) Algranati NE et al[26]**
Absorption	Rapid	rapid	sustained
Distribution	Wide	wide	Blood, organs
Clearance	----	10-fold decrease (renal and hepatic)	100-fold decrease (hepatic)
Elimination t 1/2	3-5 hours	30-50 hours	50-80 hours
Weight-based dosing	No	yes	no
Increased levels w/ multiple dosing	No	yes	yes
Protected from degradation	No	likely	yes

Table 6A. Peginterferon alfa 2b (12 kD) plus Ribavirin versus Interferon alfa 2b plus Ribavirin, as reported in the product insert,[8] and by Manns *et al*[9]				
	PEG 1.5 μg/kg per week plus ribavirin 800 mg/d		**Interferon 3mU tiw plus ribavirin 1000/1200mg/d**	
SVR (Overall)	52%[8]	54%[9]	46%[8]	47%[9]
SVRGenotype 1	41%[8]	42%[9]	33%[8]	33%[9]
SVR Genotypes 2-6	75%[8]	Genotype 2/3: 82%[9] Genotype 4/5/6: 50%[9]	73%[8]	Genotype 2/3: 79%[9] Genotype 4/5/6: 38%[9]

Table 6B. Peginterferon alfa 2b (12 kD) plus Ribavirin versus Interferon alfa 2b plus Ribavirin in Patients with Cirrhosis and Bridging Fibrosis[9]			
Treatment Group	Interferon alfa 2b (3MU thrice weekly) and ribavirin (1000 or 1200 mg daily)*	Peginterferon alfa 2b (1.5->0.5 μg/kg weekly) and ribavirin (1000 or 1200mg daily)	Peginterferon alfa 2b (1.5 μg/kg once weekly) and ribavirin (800 mg daily)
SVR rates in subjects with cirrhosis or bridging fibrosis	41% (33-50%) **(n=132)**	43% (35-51%) **(n=146)**	44% (36-53%) **(n=136)**
SVR rates in subjects with no fibrosis or portal fibrosis only	49% (44-54%) **(n=336)**	51% (45-56%) **(n=345)**	57% (51-62%) **(n=333)**

* per cent response with 95% confidence intervals; n = total number in group

Table 7A. Peginterferon alfa 2a (40 kD) versus Interferon alfa 2a in Patients with Chronic Hepatitis C[23]		
	Interferon alfa 2a SQ 6mUtiw/3mU tiw	**PEG 180 µg SQ per week**
SVR (Overall)	19%	39%
SVR (Genotype 1 > 2,000,000 HCV RNA)	1%	14%
SVR (Genotype 1 < 2,000,000 HCV RNA)	15%	44%
SVR (Genotype 2,3 > 2,000,000 HCV RNA)	30%	48%
SVR (Genotype 2,3 < 2,000,000 HCV RNA)	50%	67%

Table 7B. Peginterferon alfa 2a (40 kD) versus Interferon alfa 2a in Patients with Cirrhosis and Transition to Cirrhosis[24]			
	Interferon alfa 2a SQ 3mU tiw	**PEG 90 µg SQ per week**	**PEG 180 µg SQ per week**
SVR (Overall)	8%	15%	30%
SVR (Genotype 1)	2%	5%	12%
SVR (Genotype non-1)	15%	29%	51%

(ii) Standard interferon alfa 2b plus Ribavirin

Interferon alfa 2b and ribavirin (the combination of which is called Rebetron®) is significantly more effective than interferon monotherapy (**Table 8**).[6,7] Both interferon and ribavirin are available as monotherapy, but ribavirin is only indicated for use in chronic hepatitis C when administered in combination with interferon.

Table 8. Comparison of Treatment with Standard Interferon alfa 2b versus Interferon alfa 2b plus Ribavirin (1000-1200mg/d) Combination Therapy for 24 and 48 weeks[7]

	IFN (3mU tiw) plus placebo		IFN (3mU tiw) plus ribavirin	
	24 weeks	48 weeks	24 weeks	48 weeks
ETR (overall)	29%	24%	53%	50%
SVR (overall)	6%	13%	31%	38%
SVR Genotype 1	2%	7%	16%	28%
SVR Genotype non-1	16%	29%	69%	66%

(iii) Dose of Ribavirin in combination with interferon or peginterferon

The optimal dose of ribavirin needed to achieve maximum efficacy with tolerable side effects is under investigation. The dose most extensively studied with interferon alfa 2b is 1,000 mg qd (≤ 75 kg) and 1,200 mg qd (>75 kg), administered in two divided doses.[7] The dose studied in the peginterferon alfa-2b combination trials was 800 mg qd independent of weight.[8,9] A retrospective analysis of patients receiving either interferon alfa 2b or peginterferon alfa 2b (12 kD) (1.5 µg/kg) suggests that an improved SVR is associated with ribavirin doses greater than 10.6 mg/kg (or daily dose of greater than 795 mg for an average 70 kg man).[9] Prospective studies of weight-based dosing of ribavirin in combination with peginterferon alfa-2b are underway.

A recent study of combination therapy of peginterferon alfa 2a plus ribavirin[22] suggests that ribavirin at a dose of 800 mg is sufficient for patients infected with genotype non-1. In contrast, ribavirin at a dose of 1,000 mg qd (for weight ≤ 75kg) or a dose of 1,200 mg qd (for a weight >75kg) provides a superior response for patients infected with genotype 1 when combination therapy is administered for 48 weeks. However, incidence of dose modifications for anemia were greater in patients receiving the higher dose of ribavirin for 48 weeks than in those receiving lower doses.[22]

This study,[22] as well as the experience with standard interferon plus ribavirin,[7] indicates that ribavirin at 1,000/1,200mg based on body weight in combination with peginterferon resulted in higher sustained virologic response rates in genotype 1 infected patients.

(iv) Decision to treat with peginterferon versus standard interferon plus ribavirin

Peginterferon alfa-2b offers the convenience of once weekly versus three times weekly dosing, but peginterferon alfa-2b is associated with a greater incidence of cytopenias and injection site reactions compared with standard interferon alfa-2b.[9] Moreover, there are sub-sets of patients in which the superiority of treatment response with pegylated interferon plus ribavirin has not been demonstrated. These include patients with genotype non-1 infection (**table 6A**) and patients with compensated cirrhosis (**table 6B**).[9] When deciding whether to treat a patient with peginterferon or standard interferon in combination with ribavirin, the patient and provider should weigh the risks and benefits of the two treatment regimens. For example, in the patient with compensated cirrhosis, particularly if he/she has leukopenia prior to therapy, standard interferon alfa-2b might be the preferred treatment because of a short half-life and reduced likelihood of dose reductions for cytopenias.[9,10,27]

(v) Interferon alfa or Peginterferon Monotherapy

For patients with contraindications to the use of ribavirin, such as those with unstable cardiac disease, anemia, renal insufficiency, or those who might become pregnant (or whose sexual partners might become pregnant) on treatment or within six months of completing therapy, monotherapy with standard or pegylated interferon should be considered.[28,29]

There are five FDA-approved formulations of interferon (interferon alfa 2a, interferon alfa 2b, interferon alfa con-1, peginterferon alfa 2b (12kD) and peginterferon alfa 2a (40kD). Peginterferon alfa monotherapies have been shown to be superior to standard interferon alfa monotherapies in the treatment of hepatitis C **(tables 7A,9)**, and pegylated interferon monotherapy is the treatment of choice in select patients (see below):[29]

Table 9. Virological response to 48 weeks of treatment with Peginterferon alfa 2b (12 kD) versus Interferon alfa 2b[29]

	Peginterferon 0.5 µg/kg/wk (N=309)	**Peginterferon 1.0 µg/kg/wk (N=295)**	**Peginterferon 1.5 µg/kg/wk (N=301)**	**Interferon alfa 2b 3mU tiw (N=302)**
ETR (Overall)	33%	41%	49%	24%
SVR (Overall)	18%	25%	23%	12%
SVR (Genotype 1) (N=850)	10%	14%	14%	6%
SVR (Genotypes 2,3) (N=325)	35%	47%	49%	28%
SVR (Genotypes 4,5,6) (N=32)	20%	31%	60%	0%

Recommendations for pegylated interferon as monotherapy include

a. patients who require treatment for hepatitis C and in whom ribavirin is contraindicated:
   i. Renal insufficiency/ failure (serum creatinine > 1.5 mg/dL). Peginterferon should be used with caution in patients with creatinine clearance less than 50 mL/min.[8]
   ii. Anemia (baseline hemoglobin <13 g/dL for men, <12 g/dL for women)

iii. History of thalassemia or other hemoglobinopathies even in the absence of anemia, because of theoretical risk of precipitating profound hemolysis
iv. Significant cardiac disease (arrhythmias, angina, coronary artery bypass surgery, myocardial infarction) in the past 12 months
v. Women who may become pregnant during the course of treatment or during the six months following treatment and who refuse to use adequate contraception
vi. Men who, despite education and counseling, may cause conception of a fetus through failure to practice appropriate barrier contraception or who may donate sperm for purposes of conception

b. patients who require treatment for hepatitis C who are unable to tolerate ribavirin:
The main side effect of ribavirin is hemolytic anemia. While most patients respond to dose reductions, some patients are unable to maintain stable hemoglobin levels with any exposure to drug. Other significant adverse effects of ribavirin include nausea, vomiting, diarrhea, shortness of breath, and rashes. If these toxicities are intolerable, ribavirin must be discontinued.

Ribavirin alone has no activity on hepatitis C replication and is not indicated as monotherapy for chronic hepatitis C.

(vi) Interim summary for treatment naïve patients
In patients previously untreated with interferon or ribavirin, the following regimens are recommended:

Genotype 1: Pegylated interferon plus ribavirin 1000/1200 mg based on body weight > or ≤ 75 kg.

Genotype 2 or 3: Pegylated interferon plus ribavirin 800 mg or standard interferon plus ribavirin 1000/1200 mg based on body weight > or ≤ 75 kg; treatment decisions should be individualized based on patient preference and side effect profiles of the interferon preparations.

Treatment duration should be tailored according to infecting genotype and response to therapy (**section VIII**).

VI:B. Anti-viral therapy for previously treated patients

Limited data are available regarding treatment of patients who previously had an initial response followed by loss of virological response (relapsers) and those who were previously treated but never attained a virological response (non-responders).

Both interferon alfa 2b plus ribavirin therapy and interferon monotherapy are FDA-approved for the treatment of relapsers to interferon monotherapy.[30,31] The responses in "relapsed" patients to combination therapy for 6 months and to interferon alfa con-1 (consensus interferon) monotherapy (15 μg three times weekly) for 12 months are numerically similar (40-50%), although the two have never been compared prospectively.[30,31]

Treatment recommendations for patients who have failed to respond to interferon monotherapy or combination ribavirin therapy with either peginterferon or interferon are in evolution. For patients who have previously been treated with interferon without an initial normalization of serum ALT and/or loss of HCV RNA, further interferon plus ribavirin is only occasionally

(~10%) associated with a prolonged benefit. For patients who have failed to achieve a response to standard interferon plus ribavirin, additional therapy with pegylated interferon plus ribavirin appears to result in sustained virological response in the minority (~15-20%).[4] Patients with genotypes 2 or 3 may have better responses to retreatment than those with genotype 1 infection.[4]

Currently, no FDA-approved treatments exist for patients who have failed interferon plus ribavirin or peginterferon plus ribavirin.

Interim summary for treatment experienced patients:

- **In patients who relapsed after interferon monotherapy:**
  consider a full course of combination therapy (pegylated interferon and ribavirin for genotype 1 and standard or pegylated interferon plus ribavirin for genotype 2 or 3)
- **In patients who did not respond to interferon monotherapy:**
  further treatment with standard interferon plus ribavirin results in virological responses of only ~10%. These low responses likely do not justify retreatment. Preliminary data suggest that retreatment with pegylated interferon plus ribavirin results in a higher response (~20-25%), a response that may justify therapy.[32]
- **In patients who relapsed after combination of standard interferon and ribavirin:**
  there is insufficient information to recommend retreatment with pegylated interferon plus ribavirin.
- **In patients who did not respond to standard interferon and ribavirin:**
  further treatment with pegylated interferon plus ribavirin results in virological responses of only ~15-20%. The risks and benefits of retreatment should be evaluated for each patient on a case-by-case basis.[4] The severity of the underlying liver disease, infecting genotype and tolerability of the prior treatment regimen should be included in the decision about retreatment.[4]

VII. Monitoring on Therapy and Recommendations for Dose Reduction (see tables 10 and 11)

VII:A. Monitoring on Therapy (table 10)

The following tests should be checked at weeks 1 or 2, week 4, and at periodic intervals (approximately monthly or bimonthly**) during therapy:

- hemoglobin*
- hematocrit*
- white blood cell count with differential
- platelet count

* *Particular attention must be paid to the development of anemia in patients receiving interferon plus ribavirin therapy.*

** ***More frequent monitoring is advised in patients with either significant reductions of hematocrit, white blood cell count, or platelet count, or significant adverse events including psychiatric disease.***

Additional recommendations for monitoring patients on therapy:

- A health care provider should evaluate patients at 1-2 month intervals for treatment side effects and for guidance in managing these side effects.
- Serum ALT should be checked at month 1 and at 2-3 month intervals to monitor biochemical response.
- HCV RNA should be measured by a quantitative assay 12 weeks into treatment with interferon alfa 2b plus ribavirin or peginterferon alfa 2b (12kD) plus ribavirin in all patients. Optimal methods to measure HCV RNA are evolving. Sensitive qualitative PCR-based assays detect the presence or absence of virus, but quantitative assays can measure changes in the levels of HCV RNA. Treatment discontinuation should be considered in patients who, after twelve weeks of treatment, still have detectable HCV RNA, or who have failed to have a reduction in HCV RNA on therapy of at least 2 logs.[22]
- In all patients, HCV RNA measurement by a sensitive assay (lower detection limit of 50 IU/mL or lower) at the end of therapy and six months following therapy is necessary to determine the presence and durability of response.
- Patients not exhibiting depression before treatment should be evaluated for depression regularly (e.g. every clinic visit). Pending further empirical support, the use of a standardized questionnaire (e.g. Beck Depression Inventory, Brief Symptom Inventory)[18,19] at each clinic visit, particularly in patients with symptoms of depression is encouraged. Patients with scores above clinical cutoffs should be considered for antidepressant treatment. Mental health professionals should be consulted in such patients. Also, patients with pretreatment scores below clinical cutoffs should receive a clinical evaluation by a mental health professional if their depression scores increase during treatment.
- Urine toxicology screening may be done at each clinic visit, or as indicated, in patients with a history of a substance use disorder. Alcohol intake should be assessed monthly. Indications of an addiction relapse warrant consultation with treatment specialists.
- Adherence to therapy should be assessed through patient interviews and prescription review at every visit as non-adherence may impact response.
- To prevent the transmission of hepatitis C, patients should refrain from donating blood, organs, tissues, or semen. Safe sexual practices, including the use of latex condoms, are strongly encouraged for patients with multiple sexual partners. While transmission is rare in monogamous long-term relationships, sexual partners may wish to be tested for HCV. Patients should avoid sharing of razors or toothbrushes with household members.
- Thyroid function as measured by a serum TSH should be checked every 6 months.
- **All patients must practice adequate contraception while on interferon plus ribavirin therapy and for six months after completion of treatment. Patients and their partners should use barrier contraceptives (condoms) plus at least one other reliable form of contraception. The only exception to this is surgical sterility of greater than one year. Monthly pregnancy tests may aid in making timely decisions should a patient become pregnant while on therapy.**

Table 10. Monitoring and Modification for Interferon plus Ribavirin Combination Therapy		
Parameter	**Interval**	**Recommended Action/Comments**
Hgb, Hct, WBC/diff, and Platelet Count	Week 1 or 2, and week 4, then monthly or bimonthly during therapy. Monthly intervals are recommended in patients with values below the lower limit of normal	• **Ribavirin to 600 mg/daily:** Hgb<10g/dL *or* in cardiac pt≥2g/dL drop within a 4-wk period • **IFN to 1.5 MU tiw:** WBC <1.5, Neutrophils <0.75 *or* Platelets <50k • **Permanently discontinue both drugs:** Hgb <8.5 g/dL, WBC <1.0, Neutrophil <0.5, *or* Platelets <25K
Serum ALT	Month 1, then every 2-3 months	Monitor when doing other tests
Pregnancy Test	Monthly during therapy and for 6 months after completing therapy	Patients and partners receiving combination therapy should use barrier contraceptives plus one other form of effective contraception throughout and for 6 months after therapy. If a positive pregnancy test is confirmed, therapy should be discontinued and the outcome of the pregnancy monitored closely
HCV RNA By a quantitative assay	12 weeks on therapy	Consider discontinuing treatment for patients who remain viremic at 12 weeks and who have failed to have at least a two log reduction in viral load from pretreatment level
HCV RNA By a sensitive assay (minimum lower limit of detection of <50 IU/mL)	End of therapy and 6 months following the completion of therapy	Essential for defining on-treatment and post-treatment response
Depression screen	At each routine visit	For patients screening positive, consider antidepressant and/or Mental Health referral
Assessment for substance abuse	Monthly, if history of cocaine, opiate, or amphetamine use	If positive, refer to Addiction Specialist
TSH	Before treatment and at 6 and 12 months on treatment	If TSH becomes elevated, confirm result and consider thyroid replacement therapy
Liver Biopsy		Repeat after baseline rarely needed

VII:B. Dose Modifications

Guidelines for dose modifications of interferon plus ribavirin are summarized in **table 10** and include

- reduction of ribavirin to 600 mg daily for hemoglobin < 10g/dL in patients with a cardiac history or for > 2 g/dL drop in hemoglobin over a four-week period in all patients
- reduction of interferon to 1.5 MU tiw for WBC < 1.5, neutrophils < 0.75, or platelets less than 50k
- permanent discontinuation of both medications for hemoglobin < 8.5 g/dL, WBC < 1.0, neutrophils < 0.5, platelets < 25k

Guidelines for dose reduction/discontinuation of peginterferon alfa-2b (12 kD), given alone or in combination with ribavirin, are summarized in **table 11**.

Table 11. Guidelines for Dose Reduction/Discontinuation of Peginterferon alfa 2b (12 kD) and Peginterferon alfa 2b plus Ribavirin[8]

		Peginterferon	Ribavirin
Hgb	<10.0 g/dL	----------	Decrease by 200 mg/d.
	<8.5 g/dL	Permanently discontinue	Permanently discontinue
WBC	<1.5 X 10^9/L	Reduce Dose by 50%	----------
	<1.0 X 10^9/L	Permanently discontinue	Permanently discontinue
Neutrophils	<0.75 X 10^9/L	Reduce Dose by 50%	----------
	<0.5 X 10^9/L	Permanently discontinue	Permanently discontinue
Platelets	<80 x 10^9 /L	Reduce Dose by 50%	----------
	<50 x 10^9 /L	Permanently discontinue	Permanently discontinue

VIII. Treatment Duration

Pegylated interferon or standard interferon plus Ribavirin Therapy

- In patients receiving peginterferon alfa 2b (12 kD) therapy with or without ribavirin, there are no data regarding sustained virological responses comparing 24 versus 48 weeks of therapy because all patients included in the pivotal phase II/III trials were treated for 48 weeks.[8,9]

- Recent data with peginterferon alfa 2a suggest that 24 weeks of combination therapy (peginterferon plus ribavirin at 800 mg/d) is sufficient for patients with genotype non-1 infection,[22] but that treatment for 48 weeks with a higher dose of ribavirin is necessary for patients with type 1 infection. It is assumed but not proven that these regimens will be optimal for patients receiving peginterferon alfa 2b as part of their combination regimen.

- In patients with genotype 1 infection receiving therapy with either interferon or interferon plus ribavirin, sustained virological responses are superior in those receiving 48 weeks versus 24 weeks of therapy (**table 8**).

- In patients with non-1 infection receiving standard interferon plus ribavirin, sustained virological response is comparable in patients receiving either 24 or 48 weeks of therapy **(table 8).** The initial recommendations were to treat all non-1 patients for 24 weeks regardless of either a biochemical or virological response. However, patients with advanced disease and/or high viral loads should be considered for 48 weeks of therapy if they have a virological response at 12 weeks. Decision to treat for 48 weeks should include information about patient tolerability of the therapy and his or her ability to continue treatment for an additional 24 weeks.

- In patients receiving combination therapy with either standard or peginterferon and (i) detectable HCV RNA, (ii) and/or less than a two log drop from baseline HCV RNA levels,[21] additional treatment rarely results in viral eradication. Hence, one should consider discontinuing treatment in these patients.

Exceptions to discontinuing treatment at 12 weeks for non-responders include patients with either moderate fibrosis or cirrhosis who appear to be benefiting in part from treatment (normalization of serum ALT despite persistence of HCV RNA or a two log reduction in HCV RNA despite the persistence of HCV RNA). Such patients are clearly in need of therapy and may derive benefit from its continuation. The risks and benefits of treatment beyond one year for patients who have failed to clear virus are under investigation.

<u>Interim summary for treatment of HCV disease</u>

- Treatment duration should be 48 weeks in patients with genotype 1 infection who have an on-treatment virological response to combination ribavirin with either standard or peginterferon.
- Treatment duration should be 24 weeks in patients with genotype non-1 infection who have an on-treatment virological response to combination ribavirin with either standard or peginterferon.
- Treatment should be discontinued in patients who have failed to have a virological response by 12 weeks.
- In patients who have significant hepatic fibrosis (stage III or stage IV disease), treatment beyond 12 weeks can be considered even in the absence of a complete virological response, particularly if reduction in viral load has been observed.

IX. Erythropoietin and other Growth Factors as Potential Supportive Therapy

IX:A. Erythropoietin

The kidneys produce the hormone erythropoietin to stimulate erythrocyte production. Recombinant erythropoietin is approved by the FDA for the treatment of anemia in HIV-infected patients on zidovudine therapy,[33] patients with non-myeloid malignancies receiving chemotherapy,[34] patients with chronic renal failure,[35] and patients who are anemic prior to surgery and do not wish to be transfused.[36] Erythropoietin is not approved for anemia associated with hepatitis C therapy. Some clinicians advocate using erythropoietin for the

treatment of the hemolytic anemia observed in patients with chronic hepatitis C infection receiving ribavirin. Mean decrease in hemoglobin in patients on ribavirin is 2-3 g/dL, a fall that should lead to dose reduction of ribavirin (see **table 11**). This dose reduction, in contrast to dose discontinuation, appears to have only minor effects on reducing efficacy of therapy.[21] If erythropoietin does play a role in improving treatment response through its effects on ribavirin dosing, it seems that it would be most useful in preventing discontinuation of ribavirin in patients with profound hemolysis.

Erythropoietin has been shown to improve the ribavirin-induced anemia. In one study, 17 chronic hepatitis C patients became anemic (median hemoglobin decrease of 3.6 g/dL) during treatment with interferon and ribavirin.[37] These patients were treated with recombinant erythropoietin at a dose of 10,000 – 40,000 units SC qw. Fourteen patients continued on interferon and ribavirin as well as erythropoietin, as the median hemoglobin increased by 2.7 g/dL. Fatigue and dyspnea also either improved or resolved on treatment with erythropoietin. In an open-label, multicenter study, 44 chronic hepatitis C patients on interferon and ribavirin became anemic (hemoglobin <12 g/dL) during the first 6 months of treatment.[38] These patients were randomized to receive either epoetin alfa (erythropoietin) 40,000 units SC qw for up to 36 weeks or standard of care (ribavirin dose reduction for significant anemia). The administration of erythropoietin significantly increased the hemoglobin at latest follow-up compared to patients receiving the standard of care (mean change of 2.5 g/dL versus 0.3 g/dL, respectively; $p<0.5$). Alleviation of the ribavirin-associated anemia also permitted the administration of higher doses of ribavirin in the epoetin alfa group than in the "standard of care" group (982 mg/d versus 678 mg/d, respectively, at week 16; $p=0.003$). Erythropoietin appeared to be safe, since adverse events were similar in the epoetin alfa group and the "standard of care" group. The authors concluded that treatment with epoetin alfa was well tolerated and permitted the maintenance of "optimal" ribavirin dosing in most patients. Proof that this strategy improves SVR is lacking.

The cost-effectiveness of erythropoietin therapy and the impact of erythropoietin treatment on response rates and quality of life remain to be determined. Until such data are available, the routine use of erythropoietin for chronic hepatitis C patients who become anemic during interferon and ribavirin treatment cannot be recommended. Dose reduction of ribavirin should still be the first intervention in patients who develop anemia. Erythropoietin at a dose of 40,000 units SC qw may be beneficial in the subgroup of patients with severe symptomatic anemia (Hgb < 10 g/dL), and in those with persistent symptomatic anemia despite reduction in ribavirin dose.

Recent data support the benefit of 1000/1200mg of ribavirin in the treatment of patients with genotype 1 infection.[37-39] There are also preliminary data suggesting that erythropoietin improves a patient's ability to stay on ribavirin at full dose. Therefore, erythropoietin for treatment of ribavirin-induced anemia could be considered. Currently, there is no evidence that the use of erythropoietin to facilitate ribavirin dosing increases virological response.

IX:B. Growth Factors for Neutropenia and Thrombocytopenia

Interferon causes neutropenia and thrombocytopenia by suppressing the bone marrow production of white blood cells and megakaryocytes, respectively. Both of these cytopenias are more commonly seen in patients receiving pegylated interferon than standard interferon. The dose modifications of standard interferon and pegylated interferon for neutropenia and thrombocytopenia are listed in **tables 10** and **11**, respectively.

Granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) stimulate neutrophil production and reduce infectious complications. Both growth factors have been used for the treatment of neutropenia in HIV-infected patients[33] and in patients undergoing cancer chemotherapy.[40]

The limited data that are available on the use of recombinant G-CSF for the management of interferon-induced neutropenia in chronic hepatitis C disease and in patients with hepatitis C disease undergoing liver transplantation suggest that G-CSF increases white blood cell count and may permit administration of full-dose interferon.[41-45] Typical doses of G-CSF are 300 µg SC on Mondays and Thursdays;[43] however, the studies of G-CSF have been small and uncontrolled, and the efficacy, cost-effectiveness, and improvement in treatment responses are unproven. Until such data are available, routine use of G-CSF cannot be recommended for patients with hepatitis C disease who become neutropenic during interferon therapy.

Recombinant thrombopoietin is commercially available and has been used for the treatment of thrombocytopenia in patients undergoing cancer chemotherapy.[46] The liver produces thrombopoietin and serum levels decline with worsening liver disease.[47] One *in vitro* study has suggested that thrombopoietin may be beneficial for the treatment of thrombocytopenia caused by interferon;[48] however, clinical trials are needed to assess the safety and efficacy of recombinant thrombopoietin in this setting. Until such data are available, thrombopoietin cannot be recommended for patients with hepatitis C disease who become thrombocytopenic during interferon therapy.

X. Summary of Current Recommendations for Treatment

X:A. Treatment Naive Patients

- Peginterferon alfa 2b (12 kD) plus ribavirin: Peginterferon alfa 2b 1.5 µg/kg q week plus ribavirin 800 mg qd with a decision to continue or withdraw therapy based on virological response at 12 weeks. Patients with genotype 1 infection may benefit from higher doses of ribavirin (1,000 mg for ≤75 kg, 1,200 mg for >75 kg in two divided doses daily)

Or

- Interferon alfa 2b plus ribavirin: Interferon 3 mU tiw and ribavirin (1,000 mg for ≤75 kg, 1,200 mg for >75 kg in two divided doses daily) with a decision to continue or withdraw therapy based on virological response at 12 weeks and assessment of the clinical needs of the veteran.

Or

- Peginterferon alfa 2a (40kD): Peginterferon alfa 2a (40kD) has recently been FDA approved as monotherapy although response is lower than that observed with combination therapy with ribavirin, regardless of the type of interferon used.

In patients with genotype non-1 infection and in patients with compensated cirrhosis, interferon plus ribavirin offers the same treatment response as peginterferon plus ribavirin with fewer side effects (injection site reactions and neutropenia).

Peginterferon plus ribavirin offers improved efficacy in patients with genotype 1 infection, particularly in those with low pre-treatment HCV RNA.

- Treatment Duration

  1. Genotype 1 Infection
     Patients receiving interferon plus ribavirin (whether standard interferon or peginterferon) should be treated for 12 weeks. In those who are HCV RNA negative after 12 weeks and/or who have achieved a drop in HCV RNA level of two logs or more, treatment should be continued for a total of 48 weeks. In those with detectable HCV RNA after 12 weeks, treatment should be discontinued because a sustained viral clearance with an additional 36 weeks of therapy is rare. Exceptions to this algorithm include patients with advanced disease who could *in theory* benefit from viral suppressive therapy and patients with either a biochemical or a virological response on treatment but not both. Continued treatment for up to 48 weeks may be beneficial in these latter two groups. Benefits of treatment beyond one year in preventing long-term complications of liver disease are under investigation. Long-term suppressive therapy cannot be recommended until such data are available.

  2. Genotype Non-1 Infection
     Patients receiving standard interferon plus ribavirin should be treated for 24 weeks. In those who are HCV RNA negative after 24 weeks and have favorable characteristics of response, treatment should be discontinued. In those patients with advanced disease and/or high viral load, treatment may be continued for a total of 48 weeks. In those with detectable HCV RNA after 24 weeks, treatment should be discontinued for the same reasons and with the same provisions as described above for genotype 1 infection.
     The treatment algorithm is less well established for peginterferon plus ribavirin, but 24 weeks appears sufficient in this group.[22] Decision to stop therapy in patients without an early virological response may be made at 12 weeks in patients receiving peginterferon plus ribavirin.

- Ribavirin Dose
  In combination with standard interferon alfa 2b, the dose of ribavirin is either 1,000mg (≤75kg) or 1,200mg (>75 kg). In combination with peginterferon alfa 2b (12 kD), the dose of ribavirin is 800 mg for genotype non-1. While this is the FDA-approved dose for peginterferon for genotype 1 infection, recent data suggest that 1,000/1,200mg may result in improved response. The use of "weight-based" doses of ribavirin is under evaluation. Ribavirin is not effective as a single agent.

- Ribavirin Toxicity
  For patients who develop hemolytic anemia, the ribavirin dose should either be reduced or discontinued. Erythropoietin therapy to counter the anemia may be necessary if the patient develops moderate symptoms from the anemia, or if symptomatic anemia persists despite ribavirin dose reduction.

- Peginterferon Monotherapy as Potential First Line Therapy While there are no prospective comparisons of peginterferon alfa 2b (12 kD) monotherapy with interferon alfa 2b plus ribavirin, SVRs appear to be lower in the former than in the latter group. Peginterferon alfa 2a monotherapy has been shown to be less effective than interferon alfa 2b plus ribavirin. Thus, peginterferon monotherapy should not be administered as first line therapy in treatment naïve individuals unless the patient has contraindications to ribavirin.

X:B. Treatment Naïve Patients with Contraindications to Ribavirin

- Peginterferon Monotherapy Pegylated interferon alfa 2a (1.0μg/kg) or alfa 2a (180μg) should be given every week for one year. A decision to continue or withdraw therapy after 24 weeks is based on the virological response, regardless of the infecting genotype.

- Other Interferons as Monotherapy Given the superiority of peginterferon alfa 2b (12 kD) and peginterferon alfa 2a (40kD) over standard interferon, treatment with interferon alfa 2a, alfa 2b, alfa con-1 or lymphoblastoid interferon is no longer indicated as first line therapy in any population.

X:C. Non-Responders to Combination Therapy with Ribavirin plus Interferon alfa-2b or Peginterferon alfa-2b

- Treatment for Patients Who Have Relapsed After Interferon alfa-2b plus Ribavirin: There is no approved therapy for this indication. Re-treatment with Peginterferon plus ribavirin may be considered in the context of a clinical trial.

- Treatment for Patients Who Have Relapsed After Peginterferon plus Ribavirin: There are no approved therapies for this population.

- Treatment for Patients who are Non-Responders to Interferon alfa-2b and Ribavirin: There are no approved treatments for this population. However, pegylated alfa 2b (12 kD) interferon plus ribavirin (1,000 mg for ≤75 kg, 1,200 mg for > 75 kg in two divided doses daily) can be considered, preferably as part of an experimental protocol. Preliminary results suggest that SVR with re-treatment is low.[4]

- Treatments for Patients who are Non-Responders to Peginterferon and Ribavirin: There are no approved treatments for this population. Treatment with experimental therapies in a clinical trial should be considered.

XI. Therapies in Late Stage Clinical Development

XI:A. Peginterferon alfa 2a (40kD) plus Ribavirin Therapy

The results of a large prospective randomized trial of treatment naïve patients receiving either peginterferon alfa 2a (40kD) alone or in combination with ribavirin versus standard interferon plus ribavirin are shown in **table 12**. Peginterferon alfa 2a monotherapy was shown to be inferior to standard interferon alfa 2b plus ribavirin in producing a sustained response (**table 12**). These results are consistent with our recommendations above that peginterferon monotherapy should be used as initial treatment only for patients with chronic hepatitis C unable to tolerate ribavirin or who are known to have contraindications to ribavirin.

Peginterferon alfa 2a (40 kD) in combination with ribavirin (1000/1200 mg qd) has been shown to have superior efficacy to interferon plus ribavirin therapy (**Table 12**). The improved efficacy of peginterferon alfa 2a plus ribavirin over standard interferon plus ribavirin appears to be true for patients infected with genotype 1 as well as for those infected with genotype non-1.

Optimal ribavirin dose and treatment duration with peginterferon alfa 2a appear to differ depending on the infecting genotype.[22] In patients with genotype 1 infection the proportion of sustained virological response is highest in patients receiving 1000/1200mg of ribavirin for 48 weeks (**Table 13**), followed by groups receiving 1000/1200 mg ribavirin for 24 weeks (41%), 800 mg ribavirin for 48 weeks (40%), and 800 mg ribavirin for 24 weeks (29%). In patients infected with non-1 genotypes, neither treatment duration nor ribavirin dose affected sustained virological responses (range: 73%-78% for all treatment groups) (**Table 13**).

Until an analysis of these published results as well as an FDA analysis are available, final conclusions cannot be made regarding the safety and efficacy of these therapeutic regimens.

Of note, no direct comparison has been made between peginterferon alfa 2a with peginterferon alfa 2b, either as monotherapy or in combination with ribavirin. Thus, no definitive conclusions can be drawn regarding differences in either safety or efficacy between these two preparations.

Table 12. Peginterferon alfa 2a (40 kD) plus Ribavirin versus Interferon alfa 2b plus Ribavirin versus Peginterferon alfa 2a (40 kD) plus Placebo[10]

	PEG 180 µg per week plus ribavirin 1000/1200 mg/d	PEG 180 µg per week plus placebo	Interferon 3mU tiw plus ribavirin 1000/1200 mg/d
SVR (Overall)	57%	30%	45%
SVR (Genotype 1)	46%	21%	37%
SVR (Genotype non-1)	76%	45%	61%

Table 13. Peginterferon alfa 2a (40 kD) plus Ribavirin (800 mg or 1,000/1,200 mg) for 24 versus 48 weeks[22]				
	Peginterferon alfa-2a (40KD) 24 weeks		**Peginterferon alfa-2a (40KD) 48 weeks**	
Virological Response [no. with sustained virological response/ total (%)]	(A) Ribavirin (800 mg)	(B) Ribavirin (1000 mg or 1200 mg)	(C) Ribavirin (800 mg)	(D) Ribavirin (1000 mg or 1200 mg)
HCV Genotype 1	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271 (51%)
High viral titer (>2 million copies/mL)	8/50 (16%)	12/47 (26%)	67/190 (35%)	86/186 (46%)
Low viral titer (≤2 million copies/mL)	21/51 (41%)	36/71 (51%)	32/60 (53%)	52/85 (61%)
HCV Genotype non-1	83/106 (78%)	127/162 (78%)	81/111 (73%)	127/165 (77%)
High viral titer (>2 million copies/mL)	55/67 (82%)	80/101 (79%)	49/70 (70%)	83/108 (77%)
Low viral titer (≤2 million copies/mL)	28/39 (72%)	47/61 (77%)	32/41 (78%)	44/57 (77%)

XII. Concluding Comments

This outline represents recommendations for treatment based on available information and on treatment regimens that are currently FDA-approved. Because of ongoing research, response to treatments should improve, side effects should be reduced, and populations for whom treatment is appropriate should expand. As these advances occur, new recommendations will be made.

Therapy should be provided to those individuals who are at greatest risk for progressive liver disease and to those individuals whose quality of life is most impaired by infection with the hepatitis C virus. Therapy should also be made available to veterans seeking treatment who lack contraindications to therapy, even if they do not have advanced liver disease.

It is important that we obtain prospective data on the risks and benefits of treatment in populations such as veterans in whom infection is prevalent. Much of the data reviewed in these recommendations were derived from highly selected populations. As such, extrapolation of these outcomes data to the general veteran population is problematic.

At the same time, it is essential that we test and develop safe and effective therapies in those who have until now been inadequately served; those with contraindications to treatment with interferon or ribavirin and those in whom treatment responses are suboptimal. These include patients with renal failure on dialysis, those with advanced and decompensated HCV disease, those with difficulty adhering to injection regimens, minority populations, those with uncontrolled psychiatric disease or injection drug use, and those with HIV coinfection. In these populations, response to treatment is either lower than “standard populations” or adverse events preclude

treatment. It is likely that effective therapy will require non-interferon, non-ribavirin based therapies that are currently early in their development.

Optimization of treatment in veterans will require clinical and basic research to evaluate the safety and efficacy of available treatments. In addition, clinical research is needed to determine the natural history and morbidity resulting from this chronic viral infection.

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